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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/803,165	03/09/2001	Harald Sobek	5328	4735

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EXAMINER
SCHMIDT, MARY M

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 01/24/2003 13

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/803,165	SOBEK ET AL.	
	Examiner	Art Unit	
	Mary M. Schmidt	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 November 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 March 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Oath/Declaration

1. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c). Specifically, the address for Inventor Rossi from Naples, Italy, has a non-initialed and non-dated alteration of the street name, from "Via Hiliscola" to "Via Miliscola".

Claim Rejections - 35 USC § 103

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Claims 15-29 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Geneseq AAW29323 (the sequence in Frey et al., DE 196 11 759 A1) in view of Pisani et al. (Biochemistry) and Truniger et al. (J of Mol. Biol. and the EMBO J.) for the same reasons of record set forth in the Official action mailed 06/05/02.

Applicant's arguments filed 11/11/02 have been fully considered but they are not persuasive.

The amendments to claims 26 and 27 do not change the content of the instant rejection since they introduce no new limitations not previously addressed. Pisani et al. taught for instance overexpression of the mutant polymerases in *E. Coli* (an isolated host cell, p. 15007, paragraphs 1-5).

Response to Arguments

Applicant's response to the outstanding 35 U.S.C. 103(a) rejection of instant claims 15-29 is found on pages 4-11 of the response filed 11/11/02.

Applicant explains on page 4 that the legal standard of *prima facie* obviousness is to show three basic criteria: (1) "some suggestion or motivation, in the cited references or in the art, to modify or combine the cited references"; (2) "the cited references must provide a reasonable expectation of successfully achieving the claimed invention. That is, they must do more than make the claimed invention merely obvious to try, or obvious to experiment with.... The teaching or suggestion to make the claimed invention must come from the prior art, not Applicants' disclosure."; (3) "the prior art, either alone or in combination, must teach or suggest each and every limitation of the rejected claims."

In regards to these points, applicant further states on page 6 that "[n]either Truniger *et al.* (1996), nor Truniger *et al.* (1999), nor Pisani *et al.* teach mutation of a polymerase having at least 80% homology to SEQ ID NO:34. While characterizations of the pol/exo ratios are made in the cited references, nothing in these references discuss the suitability of any mutations for PCR.

Indeed, as noted on page 7 (3rd paragraph) of the instant specification, neither ϕ29 nor *Sso* polymerases are even suitable for PCR. While Geneseq AAW29323 teaches the expression of the polymerase having 99.1% homology to instant SEQ ID NO:34, it does not teach the mutation as in Claim 15."

Firstly, in response to applicants remarks, nowhere in claim 15, nor claims 17-27, is the limitation present that requires the polymerase to be used in PCR. Instant claim 16 states that the mutant polymerase is suitable for polynucleotide amplification; instant claim 28 states that the polymerase is used in a process for "elongation of the primer"; and claim 29 states a process for amplification of a polynucleotide template. As one of skill in the art would have recognized at the time the invention was made, there are numerous types of amplification reactions known in the prior art, and "PCR" is only one of them. Since, nowhere in the claims is the limitation for amplification by "PCR" found, application is arguing limitations not found in the claims. Furthermore, the DNA polymerization experiments carried out by Truniger et al. (1996) on page 3440, col. 1, 5th paragraph, are amplification reactions from a primer. Pisani et al. (1998) taught on page 15007, col. 2, lines 13-15, that the DNA polymerase assays were described previously in reference 11, but further explain on page 15011, col. 1, last paragraph, that the polymerase activities were tested on double-stranded DNA, using calf thymus DNA. Truniger et al. (1999) further taught in col.2, para. 3 of page 67, amplification reactions using the mutant polymerases. Thus, the prior art references did meet the claimed limitations for amplification from a primer.

Secondly, although the Truniger et al. (1996 and 1999) and the Pisani et al. references did not teach specifically the use of the sequence of instant SEQ ID NO:34, they did teach the

prevalence of the Y-GG/A motif in "nearly all eukaryotic-type DNA polymerases." (Truniger et al., 1996, page 3431, col. 1, last para.) They showed the conserved motif in 51 sequences of "eukaryotic-type" DNA polymerases and state in regards to the high homology, even between viral and bacterial, cellular and TP-primed subgroups of "eukaryotic-type" organisms, that the motif exists in the majority. They state on page 3431, col. 2, first para., that "[t]hese considerations led us to define the conserved motif as 'YxGG/A' for the whole family of eukaryotic-type DNA polymerases." Although they don't specifically include the sequence of instant SEQ ID NO: 34, a polymerase from the organism *Thermococcus aggregans*, there is a strong teaching by the prior art of the high homology of all known DNA-dependent DNA polymerases (Truniger et al., 1996, state on page 3431, col. 1, lines 1-7, that "[t]he proposal that all DNA-dependent DNA polymerases may be variations of a common structure is supported by the comparison of the protein sequences and the similarities found in the three-dimensional structure of Klenow, human immunodeficiency virus (HIV) reverse transcriptase and rat DNA polymerase β...") The instant specification as filed teaches that instant SEQ ID NO:34 is a DNA-dependent DNA polymerase (page 1). Since the same (99.1% homology) DNA-dependent DNA-polymerase was known in the prior art as taught in Geneseq AAW29323 (the sequence in Frey et al., DE 196 11 759 A1), one of ordinary skill in the art would have recognized that if the DNA-dependent DNA-polymerase taught therein had the Y-GG/A motif taught by Truniger et al. (1996 and 1999) and Pisani et al., that it was of the same general class of "eukaryotic-type polymerases" discussed by Truniger et al. (1996 and 1999) and Pisani et al. Thus, absent evidence to the contrary, and in view of MPEP 2112.01, the Geneseq AAW29323 (the sequence

in Frey et al., DE 196 11 759 A1) was a polymerase that would have been considered a "eukaryotic-type" polymerase having the Y-GG/A motif taught in Truniger et al. (1996 and 1999) and Pisani et al. Therefore, the combination of cited references taught the claimed invention.

On page 6 of the response, applicant states that "[m]oreover, Claim 19 recites the mutant polymerase of Claim 15 wherein the wild-type form of the mutant polymerase is SEQ ID NO:34.... The sequence taught by Geneseq AAW29323 varies from SEQ ID NO:34 by five amino acid substitutions (4 non-conserved mutations and 1 conserved mutation). Thus, the cited references do not teach or suggest each and every limitation of rejected Claim 19."

In response, claim 19 as written is drawn to "[t]he mutant polymerase of Claim 15 wherein...." Since the claim is drawn to a *mutant* polymerase, the rejection stands over the mutant polymerase as broadly claimed in claim 15 which does not specify what other mutations may be made in addition to the change in the Y-GG/A motif to arrive at the 80% homology to SEQ ID NO:34, and thus could include the 5 amino acid difference between instant SEQ ID NO:34 and the Geneseq AAW29323/Frey et al. sequence, since such a mutant would retain an 80% homology to SEQ ID NO:34. Claim 19 as drawn to a *mutant* polymerase as claimed in claim 19 would embrace a Y-GG/A motif mutant of the Geneseq AAW29323/Frey et al. sequence.

Applicant further states on page 7 of the response that "[t]his is not true, since Truniger *et al.* (1996) teaches that replacing tyrosine with serine to form a mutant ϕ29 polymerase results in <1% of the polymerase activity as that of wild-type ϕ29 polymerase. Truniger *et al.* (1996), p.

3433 Table 1. In other words, the tyrosine to serine mutations impedes, rather than improves, polymerization in the ϕ29 polymerase. Truniger *et al.* (1996), p. 3437."

Claim 15 states that the "tyrosine of the Y-GG/A amino acid motif is substituted with another amino acid..." but does not state what other amino acid. Truniger et al. (1996) not only taught the serine mutation that applicant points to, but also taught the Y226F (Tyrosine--> Phenylalanine) substitution "favoring polymerization (high pol/exo ratio)". They taught on page 3437, col. 2 that "interestingly,... changes in different amino acids can produce very similar phenotypes (i.e. Y226F...)." Thus, while applicant points to one change in the tyrosine of the Y-GG/A motif, Truniger et al. showed that another change, albeit more conservative, to the other aromatic amino acid phenylalanine, generated a favorable polymerase. Thus one of ordinary skill in the art would have been motivated to make the T-->F mutation for the favorable polymerase results taught by Truniger et al. (1996).

Applicant further states on page 7 of the response that "[t]o reiterate, neither Truniger *et al.* (1996) nor Truniger *et al.* (1999) suggest that mutation of tyrosine always leads to improved polymerization, since at least the mutation of tyrosine to serine impedes polymerization."

In response, there is no requirement to show that "mutation of tyrosine always leads to improved polymerization" as applicant asserts. The rejection stands on the fact that Truniger et al. (1996) does teach the result that favorable polymerization, improved pol/exo ratio, was a property of the T-->F mutation, which reads on the instant claims, since the instant claims are drawn to mutation of T to any other amino acid, including F.

Applicant states that "Of course, figure 5 of the instant application demonstrates that mutation of the tyrosine to serine in *Tag* polymerase results in improved PCR fidelity as compared to wild-type. It is difficult to reconcile how a tyrosine to serine mutation shown by Truniger et al. (1996) to impede polymerization in the ϕ29 polymerase would suggest or motivate one or ordinary skill in the art to perform a similar mutation in the *Tag* polymerase."

In response, the prior art rejection was made based on what one of skill in the art would have known at the time the invention was made, and was not made based on the teachings of the Tag polymerase experiments in the instant specification as filed. The combination of the cited references, which taught the limitations of the instant claims as written, did not need to teach PCR amplification for the reasons pointed out above. Applicant is arguing limitations not explicitly found in the claims (arguments on pages 7 and 8 of the response).

On page 8 of the response, Applicant further argues that "the effects of mutating the tyrosine residue within the Y-GG/A motif, in terms of pol and exo activities, as determined by Truniger *et al.* (1996) and Pisani *et al.* do not completely correspond to the effects obtained for the *Tag* DNA polymerase." Applicant further states that "a comparison of the exonucleolytic activity of mutants containing a tyrosine to serine substitution shows that mutant *Sso* polymerase had only 5% exonucleolytic activity relative to *Sso* wild-type, whereas mutant ϕ29 polymerase had 380% and mutant Tag polymerase 187% relative activities to their respective wild-types.... Thus, in this example, between Pisani *et al.* and Truniger *et al.* (1996) it is not clear whether mutating tyrosine would result in lower (similar to Pisani *et al.*) or greater (similar to Truniger *et al.* (1996) activity than wild-type in the *Tag* polymerase."

In response, as long as there is some motivation and some expectation of success in the art recognized by one of ordinary skill in the art, the rejection is valid. In the instant case, there is motivation provided to mutate the Y-GG/A motif of eukaryotic-type polymerases shown by Truniger et al. and expectation of success as shown by Truniger et al. for at least one of the claimed embodiments, the Y-->F mutation. Applicant is again pointing to the results, this time in Pisani et al., page 15011, Tables 1 and 2, for the Y--->S mutant. Both Truniger et al. and Pisani et al. show that the Y--->S mutation does not effect a positive change in the polymerase activity as did the Y--->F mutation.

Applicant further argues that "the effects of mutating the tyrosine in the Y-GG/A is not predictable in terms of PCR performance, since neither Sso nor ϕ29 polymerases are suitable for PCR." Again, applicant is arguing limitations not found in the claims (see the discussion above, PCR is only one type of amplification reaction, and the claims are broadly drawn to use in any type of amplification reaction).

On pages 10-11 of the response, applicant argues for unexpected success for the tyrosine to serine mutant "Tag" polymerase activity in comparison to Truniger *et al.* (1996) and Pisani *et al.* Again, however, applicant is arguing limitations not found in the claims since the claims do not specifically claim a "Tag" polymerase, but rather a mutant having 80% homology to instant SEQ ID NO:34, one kind of "Taq" polymerase from the organism *Thermococcus aggregans*. Secondly, there would have been an expectation of success in the art that a Y--->F mutation would have a positive effect on polymerase activity of the sequence taught in Geneseq AAW29323/Frey et al. since both Truniger *et al.* (1996) and Pisani *et al.* taught success

(improved polymerase ability such as improved pol/exo ratio activities) in two different types of similarly categorized eukaryotic-type polymerases, the *Sso* and ϕ29 polymerases.

Applicant specifically states on page 10 of the response to "*Compare* Instant Specification, Figure 1 (90% for mutant *Tag* polymerase) with Pisani *et al.*, p. 15011 Table 2 (68% for mutant *Sso* polymerase and Truniger *et al.* (1996), p. 3433 Table 1 (7% for ϕ29 polymerase). In looking at these figures, applicant points to the Y387F mutation of the instant "Tag" polymerase as having an Exo activity of 90%, ie. 10% less than the "WT", wild-type Tag polymerase; Pisani et al. shows in the Y495F mutant 68% exo activity compared to the "WT", wild-type Sso polymerase; Truniger et al. shows a Y226F mutant ϕ29 polymerase having 7% exo activity on dsDNA (double-stranded DNA).

It is not clear why applicant points to these data points, however, since the "exo", or exonuclease activity, is not the "pol", polymerase activity of the mutants, which is what is needed for amplification of a target nucleic acid. The lower "exo" values of the Sso and ϕ29 polymerase do not adversely effect the polymerase activities. Looking at the polymerase activities in each of the cited tables, the Y-->F mutation in ϕ29 is 710% for labeling and 101% pol/exo ratio (Truniger et al. 1996, p. 3433, Table 1); is 158% in Sso polymerase with a pol/exo ratio of 2.3 (Pisani et al. page 15011, Table 2); and is 160% pol with a pol/exo ratio of 1.77 in applicant's Table in figure 1. Thus, while applicant's show a favorable increase in polymerase activity, it is no more favorable that the increase in polymerase activity in ϕ29 and Sso polymerases taught by the prior art. Thus, no surprising results have been demonstrated in the instant specification as filed.

4. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader*, may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to *Katrina Turner*, whose telephone number is (703) 305-3413.

M. M. Schmidt
January 21, 2003

JOHN L. LeGUYADER
SUPERVISORY PATENT EXAMINER
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